

### **Amendments to the Claims**

This listing of claims will replace all prior versions, and listings, of claims in the application.

#### **Listing of Claims:**

1-37. Cancelled

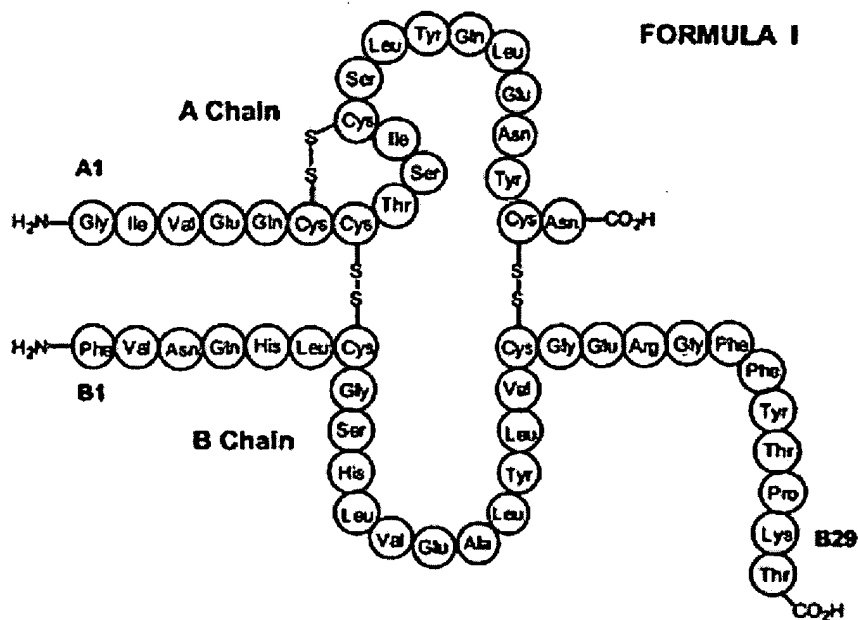
38. (Currently amended) [An] A purified insulin derivative comprising an insulin molecule and a single reactive group for covalently bonding [a] an albumin, the insulin molecule comprising an A chain and a B chain and the reactive group being a maleimido-containing group, wherein the reactive group is coupled to an  $\alpha$  amino group of the N-terminus amino acid of the B chain of the insulin molecule.

39.-40. Cancelled

41. (Previously presented) The insulin derivative of claim 38, wherein the  $\alpha$ -amino group is the  $\alpha$ -amino group of Phe B1.

42. (Previously presented) The insulin derivative of claim 38, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

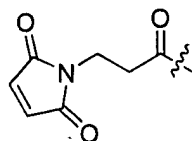
43. (Previously presented) The insulin derivative of claim 38, wherein the insulin molecule is of formula I:



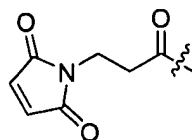
and the reactive group is coupled to an amino acid of the insulin molecule at a position Phe B1 of the insulin molecule.

44. Cancelled

45. (Previously presented) The insulin derivative of claim 38, wherein the reactive group coupled to the  $\alpha$ -amino group of the insulin molecule is:



46. (Previously presented) The insulin derivative of claim 41, wherein the reactive group coupled to the  $\alpha$ -amino group of the insulin molecule is:



47. Cancelled

48. (Previously presented) The insulin derivative of claim 38, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.

49. (Previously presented) The insulin derivative of claim 41, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.

50. (Previously presented) The insulin derivative of claim 46, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.

51. (Previously presented) The insulin derivative of claim 45, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.

52. (Previously presented) The insulin derivative of claim 48, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$  where n is an integer between 1 and 20.

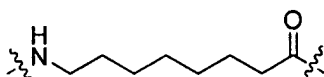
53. (Previously presented) The insulin derivative of claim 49, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$  where n is an integer between 1 and 20.

54. (Previously presented) The insulin derivative of claim 50, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy]

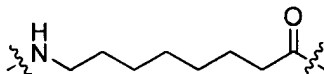
ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$  where n is an integer between 1 and 20.

55. (Previously presented) The insulin derivative of claim 51, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$  where n is an integer between 1 and 20.

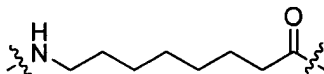
56. (Previously presented) The insulin derivative of claim 48, wherein the linker is:



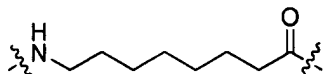
57. (Previously presented) The insulin derivative of claim 49, wherein the linker is:



58. (Previously presented) The insulin derivative of claim 50, wherein the linker is:



59. (Previously presented) The insulin derivative of claim 51, wherein the linker is:



60. Cancelled

61. (Previously presented) The insulin derivative of claim 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the  $\alpha$ -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

62. (Previously presented) The insulin derivative of claim 41, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropylcarbonyl)aminooctanamide, and wherein the  $\alpha$ -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropylcarbonyl)aminooctanamide.

63. Cancelled

64. Cancelled

65. (Previously presented) The insulin derivative of claim 38, wherein the albumin is recombinant albumin.

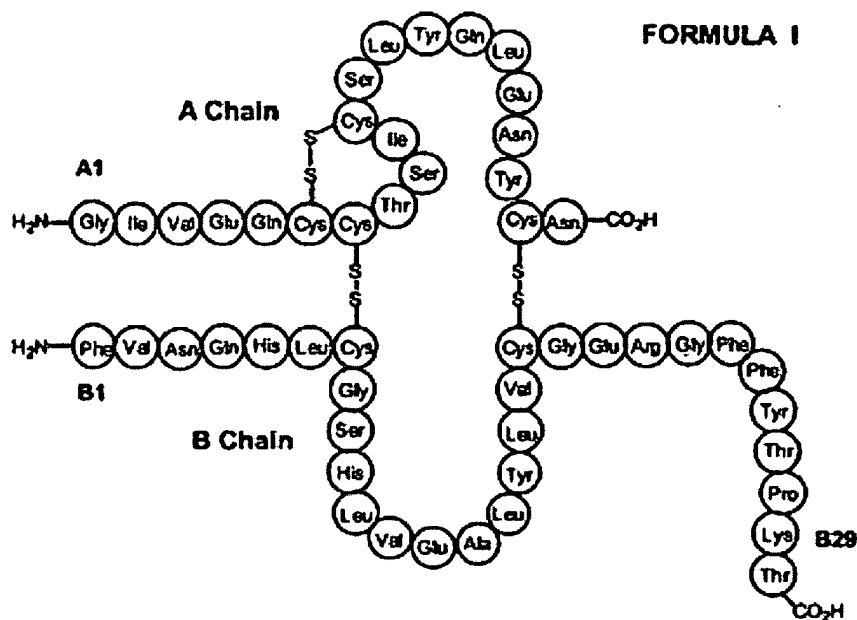
66. (Previously presented) An insulin conjugate comprising an insulin molecule, a reactive group and an albumin, the insulin molecule comprises an A chain and a B chain and the reactive group is a maleimido-containing group, wherein the reactive group is coupled to an  $\alpha$ -amino group of the N-terminus amino acid of the B chain of the insulin and wherein the reactive group is covalently bonded to the albumin.

67.-68. Cancelled

69. (Previously presented) The insulin conjugate of claim 66, wherein the  $\alpha$ -amino group is the  $\alpha$ -amino group of Phe B1.

70. (Previously presented) The insulin conjugate of claim 66, wherein the insulin molecule is selected from the group consisting of insulin glargine, insulin detemir, insulin lispro, insulin aspart and insulin glulisine.

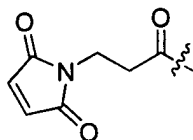
71. (Previously presented) The insulin conjugate of claim 66, wherein the insulin molecule is of formula I:



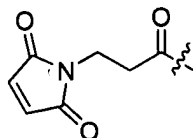
and the reactive group is coupled to the  $\alpha$ -amino group of Phe B1 of the insulin molecule.

72. Cancelled

73. (Previously presented) The insulin conjugate of claim 66, wherein the reactive group coupled to the  $\alpha$ -amino group of the insulin molecule is:



74. (Previously presented) The insulin conjugate of claim 69, wherein the reactive group coupled to the  $\alpha$ -amino group of the insulin molecule is:

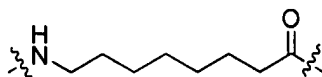


75. Cancelled

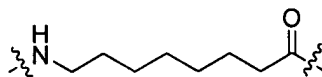
76. (Previously presented) The insulin conjugate of claim 66, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.
77. (Previously presented) The insulin conjugate of claim 69, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.
78. (Previously presented) The insulin conjugate of claim 74, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule via a linker.
79. (Previously presented) The insulin conjugate of claim 73, wherein the reactive group is coupled to the available amino group of the insulin molecule via a linker.
80. (Previously presented) The insulin conjugate of claim 76, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$  where n is an integer between 1 and 20.
81. (Previously presented) The insulin conjugate of claim 77, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$  where n is an integer between 1 and 20.
82. (Previously presented) The insulin conjugate of claim 78, wherein the reactive group is coupled to the  $\alpha$ -amino group of the insulin molecule by reacting a linker with the reactive group and the  $\alpha$ -amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2\text{-(CH}_2\text{)}_n\text{-COOH}$  where n is an integer between 1 and 20.

83. (Previously presented) The insulin conjugate of claim 79, wherein the reactive group is coupled to the available amino group of the insulin molecule by reacting a linker with the reactive group and the available amino group of the insulin molecule, and wherein the linker is selected from the group consisting of ethylenediamine (EDA), 2-[2-(2-amino) ethoxy] ethoxy acetic acid (AEEA), AEEA-AEEA and  $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$  where n is an integer between 1 and 20.

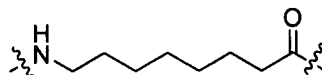
84. (Previously presented) The insulin conjugate of claim 76, wherein the linker is:



85. (Previously presented) The insulin conjugate of claim 77, wherein the linker is:



86. (Previously presented) The insulin conjugate of claim 78, wherein the linker is:



87-88. Cancelled

89. (Previously presented) The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 3-maleimidopropanamide, and wherein the  $\alpha$ -amino group of Phe is the amide nitrogen of the 3-maleimidopropanamide.

90. (Previously presented) The insulin conjugate of claim 71, wherein the insulin molecule is coupled at the terminal Phe of B1 with 8-N-(3-maleimidopropanylcarbonyl)aminooctanamide, and wherein the  $\alpha$ -amino group of Phe is the amide nitrogen of the octanamide of 8-N-(3-maleimidopropanylcarbonyl)aminooctanamide.

91-92. Cancelled

93. (Previously presented) The insulin conjugate of claim 66, wherein the albumin is recombinant albumin.

94.-115. Cancelled

116. (Previously presented) A pharmaceutical composition comprising an insulin derivative of claim 38 and a pharmaceutically acceptable carrier.

117. (Previously presented) A pharmaceutical composition comprising an insulin conjugate of claim 66 and a pharmaceutically acceptable carrier.

118. (Previously presented) A method of treating a glycaemic-related disease in a subject, comprising:  
administering to the subject an insulin derivative of claim 38, to thereby treat the glycaemic related disorder.

119. (Previously presented) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

120. (Previously presented) The method of claim 118, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

121. (Previously presented) A method of treating a glycaemic-related disease in a subject, comprising:  
administering to the subject an insulin conjugate of claim 66, to thereby treat the glycaemic related disorder.

122. (Previously presented) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes, diabetes of type I, diabetes of type II and gestational diabetes.

123. (Previously presented) The method of claim 121, wherein the glycaemic-related disease or disorder is selected from the group consisting of diabetes of type I and diabetes of type II.

124. (Previously presented) A method of making the conjugate of claim 66 *in vivo* in a subject, the method comprising administering to a subject an insulin derivative of claim 38, wherein a covalent bond between the reactive group of the insulin derivative and the albumin is formed in the subject.

125.-130. Cancelled

131. (Previously presented) The insulin derivative of claim 41, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.

132. (Previously presented) The insulin derivative of claim 38, wherein the N-terminus amino acid of the A chain and the LysB29 of the insulin molecule is Boc protected.

133. (New) A pure fraction of an insulin derivative comprising an insulin molecule connected with or without a linker to a single a maleimido-containing group for covalently bonding an albumin, the insulin molecule comprising an A chain and a B chain, wherein the maleimido-containing group is coupled to an  $\alpha$  amino group of the N-terminus amino acid of the B chain of the insulin molecule.